REMARKS

Claims 1-17, 19 and 24-63 are pending. Claims 1, 5-13, 19 and 24-37 are under examination. Claims 2-4, 14-17, and 38-63, which have been withdrawn from consideration as being drawn to an unelected invention, are being maintained of record.

CLAIMS ARE ENABLED

The rejection of claims 1, 5-13, 19 and 24-37 under 35 U.S.C. 112, first paragraph, as allegedly not being enabled, has been maintained. The Office has taken the position that "the specification, while being enabling for methods utilizing **VSV** for reducing the viability of mylogenous leukemia cell lines *in vitro*, does not provide enablement for the utilization of **VSV** for the reduction of viability of all hematopoietic tumor cells (either *in vivo* or *in vitro*)." (December 30, 2002 Office Action, page 4; May 26, 2004 Office Action, page 3) (emphasis in original). This rejection is respectfully traversed.

First, the Office has improperly sought to place on applicants the burden of proving that the invention works. This is illustrated by the following passage from the rejection with respect to the tumor cells recited in the claims:

> "Additionally, the instant claims are drawn to **all** forms of hematopoietic tumor cells, while the specification has demonstrated only two leukemia cell lines (MD7E and L1210), a couple of AML cell lines OCI/AML3 and AML5, one CML cell line (K-562) and a T-cell leukemia (MOLT-4) that are . . . susceptible to VSV infection."

(July 12, 2002 Office Action, page 4) (bolding in original, underlining added). In addition to the six cell types acknowledged by the rejection, the application also contains experimental results demonstrating that two myeloma cell types (SR and H929) are also susceptible to VSV infection. (Specification, Example 19, Table 8 on page 45).

In maintaining the rejection the Office alleges that "the specification is silent on what hematopoietic tumor cells (other than a few cell lines) are susceptible to the anti-tumor effect of VSV. . . ." (May 26, 2004 Office Action, page 5). That is wrong. All or virtually all hematopoietic tumor cells can be treated in accordance with the method of this invention. The specification further calls out leukemias, including acute myelogenous leukemia, chronic myelogenous leukemia, promyelocytic leukemia, T cell leukemia, as well as lymphomas and myelomas, as specific examples of hematopoietic tumors that can be treated in accordance with this invention. (See, e.g., original claims 5-13). It is inescapable that the alleged silence of the specification as to "what hematopoietic tumor cells . . . are susceptible to the anti-tumor effect of VSV" (May 26, 2004 Office Action, page 5) is really nothing more than the same old charge that the *in vitro* experimental evidence with eight (ungenerously characterized as a "few") tumor cell lines demonstrating anti-cancer activity that appears in the specification is allegedly insufficient to "demonstrate" efficacy.

Contrary to the clear implication of the rejection, applicants are not required to submit experimental results demonstrating the anti-tumor activity of vesicular stomatitis virus. Rather, the Office bears the burden of establishing that the specification does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated by the CCPA in In re Marzocchi:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, ___ (underlining added). It is not sufficient for the Office to simply assert that it doubts the correctness of the statements in

the disclosure. The Office must back up its doubts with evidence or reasoning. Again from In re Marzocchi:

> "In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

In re Marzocchi, 439 F.2d at 224, 169 USPQ at ___ (internal citations omitted) (underlining added). No evidence or reasoning has been cited in support of the rejection. The mere insertion of the word "only" before a list of what applicants have shown experimentally does not qualify as acceptable evidence or reasoning to sustain an enablement rejection. To the contrary, the demonstrated success in a variety of hematopoietic tumor cells supports applicants' position that the invention works for its intended purpose.

There are ample data supporting the claim that hematopoietic cancers are, in general, appropriate targets for therapy with VSV (see Table A below which summarizes data within the specification). Six different classes of hematopoietic cancer cell lines were tested in many different experiments and found to be susceptible to VSV including megakaryocytic leukemia, lymphoid leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, T cell leukemia and myeloma (Table A below). Further supporting evidence within the application is provided by the breadth of tumor cell types that are shown to be sensitive to VSV-mediated killing. The data in Table 1 of the application show that a broad panel of tumor cell types is sensitive to killing by VSV. Together, the data within the specification demonstrates that a wide variety of tumor cell types, and specifically hematopoietic cancers, are appropriate targets for therapy with VSV.

Table A. Diverse Hematopoietic Cancers Were Found to be Sensitive to VSV as Indicated in the Specification.

Cell Line Sensitive to VSV	Type of hematopoietic cancer	Data in Specification
MO7E	Megakaryocytic Leukemia	(1) Table 1 (2) Example 2:"Two leukemia cell lines MO7E and L1210; Table 1) were killed following an overnight infection and produced large amounts of virus." (page 30 lines 11-12); (3) Specification (page 19, lines 29-31): "In contrast two leukemia cell lines (MO7E and L1210) were also tested and found to be susceptible to VBV infection as evidenced by cytopathic effect, virus growth and loss of cell viability."
L1210	Lymphoid Leukemia	As noted above.
AML5	Acute Myelogenous Leukemia	(1) Specification (page 29, lines 12-14): "Other cell lines, including a lung carcinoma cell line (LC80) and a leukemia cell line, AML5 (acute myelogenous leukemia 5) cells were also found to be effectively killed by VSV."
AML3	Acute Myelogenous Leukemia	(1) Example 14 AML3 cells die by apoptosis following infection with VSV. See entire example. (2) Example 15 Mutant VSV strains infect and kill AML cells. See entire example. (3) Example 26 Selective killing of AML cells co-cultured with normal bone marrow; Also see Table 10.
Primary acute	Acute Myelogenous Leukemia	(4) Specification (page 30, lines 25-26): "These results demonstrate VSV is able to

myelogenous leukemia		preferentially kill primary leukemia blast cells while sparing normal blood cells."
K-562	Chronic Myelogenous Leukemia	Example 19 and Table 8. "This example shows that VSV is able to infect and kill a diverse set of leukemia cell types."
MOLT-4	T Cell Leukemia	Example 19 and Table 8
SR	Myeloma	Example 19 and Table 8
H929	Myeloma	Example 19 and Table 8

Additional research performed after the filing of the application demonstrates that six additional hematopoietic cancer cell lines (LY-8 B-cell lymphoma; LY-18 B-cell lymphoma; Jurkat acute lymphoblastic leukemia; OCI-My10 myeloma; OCI/AML1 acute myeloid leukemia; H191 acute myeloid leukemia) were all sensitive to killing by VSV (Lichty et al. 2004, Human Gene Therapy 15:821-31).

Moreover, the specification teaches the method by which one skilled in the art would screen a particular hematopoietic cancer to confirm its sensitivity to VSV. The level of routine testing taught in the application is well within the capabilities of one skilled in the art, and would not require undue experimentation. All of the components required for testing are disclosed and no special or unique manipulations are involved.

Second, although the July 12, 2002 Office Action focused on the supposed failure of the application to demonstrate that a wider variety of hematopoietic tumor cells are susceptible to VSV infection as seen from the above-quoted passage from page 4 of the July 12, 2002 Office Action, the December 30, 2002 Office Action proceeded to cast the rejection as one of alleged failure to name a sufficient number of hematopoietic tumor cells. Thus the rejection states:

> As outlined in the previous Office action, the instant claims are drawn to using VSV to all forms of hematopoietic tumor cells, while the

> specification is silent on what hematopoietic tumor cells (other than a few cell lines) are susceptible to the anti-tumor effect of VSV. . .

(December 30, 2002 Office Action, page 5) (emphasis in original). As seen from the above-quoted passage from the Office Action the rejection criticizes the application for not naming all of the different types of hematopoietic tumor cells. This ground of rejection is not well taken since it is well-established that "a patent need not teach, and preferably omits, what is well known in the art." (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, ___ (Fed. Cir. 1986), *citing* Lindemann Maschinenfabrik v. American Hoist and Derrick, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

The specification teaches that "VSV has a broad host range and is capable of infecting most types of human cells, whereas other viruses are more limited in regard to the types of cells they may effect". (Specification, page 6, lines 27-29). In view of the broad host range of VSV, the person of ordinary skill in the art would not require undue experimentation to practice the invention.

The Office now denies that the rejection is based on the naming of an allegedly insufficient number of hematoipoietic tumor cell types. Instead it first assumes, without foundation, that VSV does not possess antitumor activity against hematopoietic tumors generally and then faults applicants for not providing guidance as to which hematopoietic tumors are susceptible and which are immune to the antitumor effects of VSV. Thus the rejection states:

> [C]ontrary to Applicant's assertion, the rejection is based (in part) on the failure of the specification to provide guidance as to which hematopoietic tumor cells **are susceptible to the anti-tumor effect of VSV**. This is quite different from a recitation of which cells would be histologically classified as being hematopoietic in origin.

(May 26, 2004 Office Action, page 6) (bolding in original). This position would be well taken if VSV lacked antitumor activity against hematopoietic cancers generally.

However, since VSV has antitumor activity against all or virtually all hematopoietic tumor cell types, a list of the hematopoietic tumor cells that are susceptible to the anti-tumor effects of VSV would be identical or virtually identical with a recitation of hematopoietic tumor cells. Applicants chose not to unnecessarily burden the specification in this way, for which they deserve praise rather than criticism. As disclosed in the specification, eight hematopoietic cancer cell lines and one primary hematopoietic cancer comprising six different histological types including both myeloid and lymphoid lineages were tested and all were found to be sensitive to VSV. Myeloid and lymphoid lineages comprise the overwhelming majority of hematopoietic lineages. The experimental results disclosed in the specification are, therefore, more than ample evidence to support a claim for treating hematopoietic cancers generally.

Third, the Office has also improperly tried to place on applicants the burden of proving that the invention works *in vivo*. The rejection stated:

> "Claims 32-34 are drawn to the *in vivo* application of the claimed methods. People of skill in the art require documented evidence that a benefit can be derived by the therapeutic application of a given substance; however a survey of the relevant art does not indicate that substances such as those claimed provide such benefit."

(July 12, 2002 Office Action, page 4). (To avoid possible confusion arising from the above-quoted passage in the Office Action applicants note that all of the claims encompass *in vivo* administration, not just claims 32-34.) Based on the above-quoted passage from the rejection, one might think that the application contains no *in vivo* results, but it does. The specification contains *in vivo* data demonstrating the efficacy of VSV in treating human melanoma xenografts in nude mice. (Example 25, page 49).

In maintaining the rejection the Office argues that "the example recited by Applicant is insufficient to provide enablement for the full breadth of the instant claims." (May 26, 2004 Office Action, page 6). It is contrary to the law to require that enablement be provided by a single example, taken in isolation. Rather it is the specification as a whole

that must enable the claimed invention. (35 U.S.C. §112, first paragraph). Thus, it is improper to take the examples one-by-one as the rejection has done, purport to find each one insufficient to enable the full breadth of the claimed invention, set it aside, and then repeat the process with the remaining examples. Moreover, the faults the rejection purports to find with Example 25 are not well taken.

The rejection stated that the demonstrated efficacy of "two mutated VSV viruses [against] cell-line based xenographs in immunodeficient mice. . . cannot be extrapolated to the use of wild-type (non-mutated) VSV against established tumors in an immunocompetent animal." (May 26, 2005 Office Action, page 6). Cell lines implanted into athymic mice are not only an acceptable model but a standard by industry and the National Cancer Institute (NCI) for determining antitumor efficacy of a novel anticancer agent. Three anticancer agents recently approved by the U.S. FDA had earlier showed activity against xenografts of human tumor cell lines (Table B). While no model is perfect, Winograd concluded that there is "a good predictability of a panel of human tumor lines for clinically effective drugs" and that "the application of human tumor xenografts in anticancer drug development is warranted." (B. Winograd, et al., "Human tumor xenografts in the nude mouse and their value as test models in anticancer drug development (review)" In Vivo (1987) 1: 1-14, Abstract on p. 1). In the oncology reference Cancer Principles & Practice of Oncology (2001; 6th edition; editors: DeVita VT, Jr; Hellman S, and Rosenberg SA)), Chu et al (Section 19.2, para. bridging pp. 352-353) indicate that as part of the standard NCI development scheme for new cancer drugs, the human tumor cell line most sensitive to an active candidate *in vitro* is selected for testing *in vivo* as a xenograft in a subcutaneous implant site in a nude mouse. The U.S. FDA accepts positive tumor xenograft results as a sufficient level of preclinical activity when approving a clinical trial for an investigational new drug (IND).

Table B. The Sensitivity of Human Tumor Xenografts in Athymic, Nude Mice to Recently FDA-Approved Cancer Agents

Recently Approved Cancer Drug	Indication	Effects in Athymic Nude Mouse Tumor Model	References
Gefitinib (Iressa, a small molecule inhibitor of EGFR)	Lung cancer	Potent activity against human lung cancer xenograft model	Raben D, et al., Semin Oncol. 2002 Feb;29(1 Suppl 4):37-46.
Bortezomib (PS-341, a proteasome inhibitor)	Myeloma	Significant in vivo antimyeloma activity in human tumor xenograft model	LeBlanc R, Cancer Res. 2002 Sep 1;62(17):4996-5000
Cetuximab (Erbitux, a monoclonal antibody against EGFR) in combination with irinotecan	Colorectal cancer	Regressions of human colorectal cancer xenografts noted with the combination of cetuximab and irinotecan	Prewett MC et al., 2002, Clin Cancer Res 8:994-1003

The rejection stated that "said example only utilizes two of the five VSV mutants disclosed in the instant Specification lending support to the unpredictability of the anti-tumor effect of VSV." (May 26, 2004 Office Action). While Example 25 uses 2 mutant strains of VSV, the five mutants disclosed in the specification were tested in Example 20 and all five were found to have *in vitro* antineoplastic activity. Example 20 demonstrates that all five strains are selective at *in vitro* killing of tumor cells compared to normal cells. The testing of two VSV mutants in Example 25 and finding potent systemic activity with both of them only adds to the predictability of the anti-tumor effects of VSV

and does not undermine it. It would be unreasonable to conclude that the other three mutant strains would not work.*in vivo*.

Moreover, the rejection has tried to shift the enablement burden to applicants by putting the Office's unsupported doubts in the mouth of "people of skill in the art" who are said to "require documented evidence that a benefit can be derived by the therapeutic application [i.e. *in vivo*] of a given substance." (July 12, 2002 Office Action, p. 4). This citation to "people of skill in the art" obscures such crucial issues as which people require such evidence, whether they are a minority or a majority of those of skill in the art, what evidence would they consider adequate, and the purpose for which they require such evidence. The purpose for which they allegedly require the evidence is necessary to avoid improperly importing into the enablement context the more stringent requirements under the Food and Drug Act for approval to market a therapeutic agent. It is, of course, important not to confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." In re Brana, 51 F.3d 1560, 1567, 34 USPQ2d 1436, _____ (Fed. Cir. 1995), citing, Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

The Office responds that it "is not requiring Applicant to demonstrate that the claimed VSV composition is 'safe and effective' as required by the Food and Drug Act, merely that the application of said composition to an individual is beneficial to said individual." (May 26, 2004 Office Action, page 6). Thus the Office has confirmed that it is attempting to require applicants to demonstrate that the invention is "beneficial to [the] individual", a kind of super-utility standard, contrary to the law which places on the Office the burden to show otherwise. In re Marzocchi, 439 F.2d 220, 223-224, 169 USPQ 367. Even if the Office is applying a less rigorous standard than the FDA, it is nevertheless exceeding the mandate conferred on the PTO by the patent laws.

The Office has attempted to require applicants to prove that the *in vitro* data contained in the specification correlate to an *in vivo* benefit. The rejection stated:

> "[T]he specification . . . does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said viruses are administered *in vivo* to 'treat' hematopoietic tumor cells, although *in vivo* use is clearly encompassed by the claims. Lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating *in vitro* data as exemplified with *in vivo* benefit, the specification cannot be said to teach how to use the claimed viruses as pharmaceuticals."

July 12, 2002 Office Action, paragraph bridging pages 4-5. Applicants respectfully submit that it is accepted in the art to which this invention pertains that *in vitro* evidence of antitumor effect on tumor cell lines is reasonably correlated to *in vivo* therapeutic efficacy. This is shown by the Winograd paper discussed above, and the accepted utility of the NCI Tumor Cell Panel also discussed above, which demonstrates that cell culture-based assays provide are correlated with clinical utility. The correlation is further illustrated by the Pecora, et al. article submitted previously. It is also illustrated by U.S. Patent No. 5,677,178 (McCormick). The only experimental results contained in McCormick are the results of *in vitro* testing (Patent No. 5,677,178, column 18, line 42 to column 20, line 23; and Figures 2A-3C). Neverthless McCormick bases his teaching of human therapy on those *in vitro* results (Patent No. 5,677,178, column 16, line 45 to column 18, line 25). The Office attempts to devalue the importance of McCormick by noting that "it is well settled that whether similar claims have been allowed to others is immaterial." (May 26, 2004 Office Action, page 8). That statement of the law is fair enough, but it misses the point that applicants do not cite McCormick for its status as an issued patent, but rather for the fact that it illustrates that McCormick, like so many others, considered *in vitro* results to support his teaching of human therapy. The rejection also reminds applicants that "neither Pe[]cora et al. nor McCormick disclose the use of VSV for the treatment of hematopoietic tumor cells." (May 26, 2004 Office Action). But, of course the arguments of the rejection are not specific to VSV either, but rather relate to the alleged difficulty of correlating *in vitro* results to *in vivo* efficacy in the

cancer field generally. Thus, the citations to Pecora and to McCormick are properly cited to refute the rejection.

In maintaining the rejection the Office has cited several articles, which together demonstrate nothing more than the unsurprising observation that the *in vitro* environment cannot duplicate the *in vivo* environment exactly. Nevertheless, it is undeniable that *in vitro* experiments continue to be performed and relied upon to identify treatments for *in vivo* use. If the rejection was correct that "clinical correlations are generally lacking", *in vitro* experiments would not be as widely used as they are.

Moreover as mentioned above, the specification does contain *in vivo* data demonstrating the efficacy of VSV in treating human melanoma xenografts in nude mice. (Example 25, page 49). These results support applicants' position that the *in vitro* activity of VSV is correlated with *in vivo* efficacy.

Fourth, initially the Office improperly sought to place on applicants a separate burden of explaining the mechanism by which the claimed invention works. This rejection stated, "The specification is silent on what receptor is utilized by VSV for cell entry." (July 12, 2002 Office Action, page 4). As seen from the above-quoted passage, the Office has taken the position that the specification is required to explain how the viruses of the claimed invention enter the cells that they infect. That position is contrary to law because, "it is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests, nor is the inventor's theory or belief as to how his invention works a necessary element in the specification to satisfy the enablement requirement of 35 U.S.C. §112." Cross v. Iizuka, 753 F.2d 1040, 1042, 224 USPQ 739, ____ (Fed. Cir. 1985), citing Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570, 219 USPQ 1137, 1140 (Fed. Cir. 1983). In response the Office acknowledged that there is no requirement to disclose the receptor. Instead it now states that "the Specification[']s silence with regard to what receptor was utilized by VSV was merely an illustration of the total lack of guidance provided by the specification with

regard to what types of hematopoietic tumor cells could be treated by the methodologies of the instant invention". (December 30, 2002 Office Action, pages 7-8). Since it is now admitted that there is no requirement to disclose the receptor, the absence of such disclosure is actually an illustration of the sort of thing that is not part of applicants' enablement requirement in accordance with Section 112, first paragraph. The guidance provided by the specification as to the tumor cells that can be treated in accordance with this invention is discussed above.

Fifth, the Office has improperly sought to build an enablement rejection out of qualified statements in the specification concerning mechanism. The rejection stated, "The invention is predicated on the susceptible tumor cells lacking PKR activity, but the specification is silent on which hematopoietic tumor cells lack said function." (July 12, 2002 Office Action, page 4). Contrary to the above-quoted assertion from the rejection, applicants' invention is not limited to tumor cells that lack PKR activity. No such limitation appears in claim 1. The statement in the specification that "[p]referably the tumour cell lacks PKR activity" (Specification, page 4, lines 8-9) (underlining added) and the recitation of tumor cells lacking substantial PKR activity in dependent claims 18 and 19 are further evidence that the invention as a whole is not "predicated on the susceptible tumor cells lacking PKR activity". Understanding the instant invention as being "predicated on the susceptible tumor cells lacking PKR activity" is all the more unreasonable in view of applicants' express warning that their discussion of PKR's possible role was being advanced "[w]ithout being bound by theory" (Specification, page 14, lines 14-18, esp. line 14).

The Office has responded that "the specification only provides guidance for the selective in vitro killing of a few PKR- cell lines." (December 12, 2002 Office Action, page 8). That is wrong. The rejection once again confuses guidance with examples proving efficacy. The specification does provide guidance for practicing the full scope of the invention. The Office is once again attempting, contrary to the law, to impose on applicants the burden of proving effectiveness.

Sixth, the Office has faulted the specification for allegedly being silent with regard to interferon and to routes of administration. The rejection stated:

> "[T]he specification is . . . silent on which interferon other than alpha interferon would provide normal cells protection from viral infection. . . . [T]he specification is . . . silent on how said viruses are to be administered to said subject."

(July 12, 2002 Office Action, page 4). The reference to interferon presumably applies only to claims 24 and 37, which recite interferon. In accordance with this invention any interferon can be utilized. The invention as claimed does not rest on the selection of certain types of interferon. The Office has responded that "the specification is silent on the optional use of any interferon other than alpha interferon." (December 12, 2002 Office Action, page 8). As seen from the above-quoted passage from the Office Action the rejection criticizes the application for not naming all of the different types of interferon. This ground of rejection is not well taken since it is well-established that "a patent need not teach, and preferably omits, what is well known in the art." (Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, ___ (Fed. Cir. 1986), *citing* Lindemann Maschinenfabrik v. American Hoist and Derrick, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In maintaining the rejection the Office alleges that "the Office is not requiring the naming of all the different types of interferon, [rather it is requiring Applicant] to provide guidance as to which interferons other than alpha interferon would provide normal cells protection from viral infection." (May 26, 2004 Office Action, page 9). In accordance with the method of claims 24 and 37 all interferons can be utilized to provide protection against viral infection. It is well known that the "collective designation of interferons (IFN) is based on their capacity to induce antiviral activity against a broad spectrum of mammalian viruses." (Meager, "Review: Biological assays for interferons", J. Immunol. Meth. (2002) 261:21-36, on page 22, left col.).

With respect to how the virus is administered to a subject, all conventional techniques and routes of *in vivo* administration can be utilized. Other than claim 32, the invention as

claimed does not rest on the selection of certain routes of administration from among those known in the art.

The allegation that "the specification is . . . silent on how said virus is to be administered . . ." (May 26, 2004 Office Action, page 5) is wrong. The specification does indeed provide numerous examples of the successful administration of VSV by a variety of routes: intravenous injection (Example 25), by intratumoral injection (Examples 5, 16 and 18) and by injection of virus-producing cells into the tumor (Examples 5 and 16).

Both the specification and the published literature since then from the inventors and verified by other academic researchers (see Table C below) have solidified the concept that efficacy is achievable for VSV using many different routes of administration to treat a diverse set of tumors at a variety of locations.

Table C. Various routes of VSV administration are efficacious against malignancies in mice

Route	Citation
Intravenous injection	Specification: Example 25 (and Figure 13)
Intravenous injection	Stojdl DF et al., 2003. Cancer Cell 4:263-275.
Intravenous injection	Balachandran S et al., 2001 J Virol 75:3474-79
Intratumoral injection	Specification: Examples 5, 16, and 18; and Figures 5, 7, and 9.
Intratumoral injection	Balachandran S et al., 2001 J Virol 75:3474-79
Intratumoral injection	Huang T-G et al., 2003 Mol Ther 8:434-40.
Intratumoral injection	Ebert et al., Cancer Res 63:3605-11
Intratumoral treatment with cells infected with VSV	Specification: Examples 5 and 16.

In support of its contention that conventional methodologies to administer VSV would not be suitable for achieving anti-cancer effect, the rejection ignores the anti-cancer evidence in the specification and instead attempts to enlist evidence from the specification relating to toxicity. The rejection states:

> Applicant argues that all methodologies known in the art would be effective. This however, contradicts Applicant's assertion in the Specification. Applicant states on page 33 of the specification that PKR-/- mice were killed with vsv by several routes of infection but that these mice were not affected by intravenous injections of the virus.

(May 26, 2004 Office Action, page 5). The contention that the differing toxicities observed in pkr-/- mice following administration of VSV by various routes of administration equates with a similar dependence on route for the intended anti-cancer activity is invalid. Toxicity and efficacy are very different and independent endpoints. The lack of intravenous toxicity does not in any way imply that there would be a lack of efficacy by this route. Indeed, the specification demonstrates efficacy by the intravenous route (Experiment 25).

The rejection further argues that the observed difference in toxicity between the intravenous and other routes of administration "illustrates that the route of administration. . . has an affect [sic] on the biological effects of VSV in vivo." (May 26, 2004 Office Action, page 5). Any differences are likely due to dosing, and dose ranging is well within the skill of clinicians.

Next, the rejection cites Jain, Scientific American (July 1994) for the proposition that there are various impediments to delivery of drugs into solid tumors (December 30, 2002 Office action, pages 5-6). While the issues cited in the Jain article may be theoretically interesting, it is important to bear in mind that many anti-cancer drugs have been demonstrated to be effective against solid tumors even when administered intravenously. Moreover, the Jain reference suggests that solid tumors could present a greater hurdle for delivery than leukemia, but any potential impediment for the delivery of VSV to solid

tumors has already been overcome using intravenous VSV treatment of solid subcutaneous tumors as illustrated in example 25. Additional results cited in Table C (above) further confirm that VSV has antitumor efficacy when given intravenously to solid tumors in mice.

Moreover, the specification does contain *in vivo* data demonstrating the efficacy of intravenous VSV in treating human melanoma xenografts in nude mice. (Example 25, page 49). Thus in contrast to the rejection's reliance on theoretical concerns that may or may not be valid in any particular case, the specification contains actual experimental results demonstrating the anti-tumor efficacy of VSV administered intravenously.

In view of the foregoing, applicants respectfully submit that the enablement rejection is improper and should be withdrawn.

CLAIMS NOT INDEFINITE

The rejection of claims 1, 5-13, 19, and 24-37 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite, has again been maintained. This rejection is respectfully traversed. The rejection maintains two grounds of rejection, each of which is addressed by applicants in turn as follows:

1) The rejection stated that claim 1 is rendered vague and indefinite by the use of the term "administering to the tumor cell a virus". The rejection stated that it "is unclear what is meant by said term. Is said virus 'injected' into said tumor cell or merely introduced into said cells [sic] environment?" (July 12, 2002 Office Action, page 5). In accordance with this invention, the virus can be administered to the tumor cell utilizing any conventional technique. Of course, "breadth is not to be equated with indefiniteness." In re Miller, 441 F.2d 689, 693, 169 USPQ 597, ____ (CCPA 1971).

In maintaining the rejection the Office previously stated:

> Applicant's arguments have been fully considered and deemed non-persuasive. It is still unclear what is meant by said phrase. What are considered to be conventional methods of "administering"? As written, it is still impossible to determine the metes and bounds of the claimed invention.

(December 30, 2002 Office Action, page 9). In response, applicants argued that the person of ordinary skill in the art who is doing something to cells with a vesicular stomatitis virus would have no difficulty in determining whether what he is doing is "administering" the virus or not. Accordingly, those skilled in the art will be in no uncertainty concerning what subject matter falls within the scope of the claims. (In re Miller, 441 F.2d 689, 693, 169 USPQ 597, ____ (CCPA 1971)). Section 112, second paragraph, requires nothing more.

In again maintaining the rejection the Office has now clarified its reasoning, from which it is now apparent that the rejection is based on improperly reading into the claims a limitation not found therein. The rejection stated:

> The instant claim encompasses *in vivo* treatment methods. How does one specifically administer VSV directly "to the tumor cell" when said cell resides within an individual.

(May 26, 2004 Office Action, page 10) (underlining added). As seen from the passage quoted above, the rejection is based on the alleged lack of clarity as to the metes and bounds of the term "directly", a limitation that appears nowhere in claim 1. Claim 1 does not require that the virus be administered directly to the cell, only that it be administered to the cell. Both direct and indirect administration are encompassed by the scope of claim 1. Thus, there is no need to characterize a given act of administration as "direct" or "indirect" in order to determine whether it is encompassed by the claim.

The rejection presents no separate reasons for the rejection of claims 5-13, 19 and 25-37. Therefore it is believed that they are rejected under Section 112, second paragraph, solely

because they depend, either directly or indirectly, from claim 1. Accordingly, upon withdrawal of the rejection of claim 1 under Section 112, second paragraph, the rejection of claims 5-13, 19 and 25-37 should be withdrawn as well. It is believed that claim 24 has been rejected under Section 112, second paragraph because it depends, indirectly, from claim 1 and also for a separate reason, addressed below.

2) The rejection stated that claim 24 is rendered vague and indefinite by the use of the term "administering interferon to the tumor cell". The rejection stated that it "is unclear what is meant by said term. Is said virus [sic, interferon] 'injected' into said tumor cell or merely introduced into said cell[']s environment?" (July 12, 2002 Office Action, page 6). In accordance with this invention, interferon can be administered to the tumor cell utilizing any conventional technique. Again, "breadth is not to be equated with indefiniteness." In re Miller, 441 F.2d 689, 693, 169 USPQ 597, ____ (CCPA 1971).

In maintaining the rejection the Office previously stated:

> Applicant's arguments have been fully considered and deemed non-persuasive. It is still unclear what is meant by said phrase. What are considered to be conventional methods of "administering"? As written, it is still impossible to determine the metes and bounds of the claimed invention.

(December 30, 2002 Office Action, page 10). In response, applicants argued that the person of ordinary skill in the art who is doing something to cells with interferon would have no difficulty in determining whether what he is doing is "administering" or not. Accordingly, those skilled in the art will be in no uncertainty concerning what subject matter falls within the scope of the claims. (In re Miller, 441 F.2d 689, 693, 169 USPQ 597, ____ (CCPA 1971)). Section 112, second paragraph, requires nothing more.

In again maintaining the rejection the Office has now clarified its reasoning, from which it is now apparent that the rejection is based on improperly reading into the claims a limitation not found therein. The rejection stated:

> The instant claim encompasses *in vivo* treatment methods. How does one specifically administer interferon directly "to the tumor cell" when said cell resides within an individual.

(May 26, 2004 Office Action, page 11) (underlining added). As seen from the passage quoted above, the rejection is based on the alleged lack of clarity as to the metes and bounds of the term "directly", a limitation that appears nowhere in claim 24. Claim 24 does not require that the interferon be administered directly to the cell, only that it be administered to the cell. Both direct and indirect administration are encompassed by the scope of claim 24. Thus, there is no need to characterize a given act of administration as "direct" or "indirect" in order to determine whether it is encompassed by the claim.

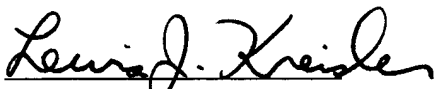
In view of the foregoing remarks, applicants respectfully submit that the remaining rejections under Section 112, second paragraph, are improper and should be withdrawn.

CONCLUSION

Reconsideration and withdrawal of all rejections is respectfully requested.

It is believed that no fee, other than the extension of time fee, is required in connection with the filing of this Communication. If any additional fee is required, the Commissioner is hereby authorized to charge the amount of such fee to Deposit Account No. 50-1677.

Respectfully submitted,



Lewis J. Kreisler
Reg. No. 38522
Attorney for Applicant(s)

930 Clopper Road
Gaithersburg, MD 20878
Phone: (240) 631-2500 x3276
Facsimile: (240) 683-3794

Enclosures:

Lichty, et al., Human Gene Therapy (2004) 15:821-831.
Winograd, et al., In Vivo (1987) 1:1-14.
Chu, et al., "Cancer Drug Development" in Cancer: Principles & Practice of Oncology, DeVita, et al. eds. (2001) Section 2, pp. 345-356.
Raben, et al., Semin. Oncol. (2002) 29(1) Suppl. 4: 37-46.
LeBlanc, et al., Cancer Res. (2002) 62:4996-5000.
Prewett, et al., Clin. Cancer Res. (2002) 8:994-1003.
Meager, J., Immunol. Meth. (2002) 261: 21-36.
Stojdl, et al. Cancer Cell (2003) 4: 263-275.
Balachandran, et al., J. Virol. (2001) 75(7): 3474-3479.
Huang, et al., Molec. Therapy (2003) 8(3): 434-440.
Ebert, et al., Cancer Res. (2003) 63: 3605-3611.